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Patent- og Varemærkestyrelsen
Økonomi- og Erhvervsministeriet

13 August 2003

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PATENT- OG VAREMÆRKESTYRELSEN

DIAZABICYCLONONANE AND -DECANE DERIVATIVES AND THEIR USE AS OPIOID RECEPTOR LIGANDS

TECHNICAL FIELD

This invention relates to novel diazabicyclononane and -decane derivatives useful as opioid receptor ligands. More specifically, the invention provides compounds useful as μ opioid receptor ligands.

In other aspects the invention relates to the use of these compounds in a method for therapy, such as for the treatment of pain, and to pharmaceutical compositions comprising the compounds of the invention.

BACKGROUND ART

Numerous classes of opioid receptors exist. These classes differ in their affinity for various opioid ligands and in their cellular and organ distribution. Moreover, although the different classes are believed to serve different physiological functions, there is a substantial overlap of function, as well as distribution. Three different types of opioid receptors have been identified, the mu (μ), delta (δ) and kappa (κ) opioid receptor. These three opioid receptor types are the sites of action of opioid ligands producing analgesic effects. However, the type of pain inhibited and the secondary functions vary with each receptor type. The μ receptor is generally regarded as primarily associated with pain relief, and drug or other chemical dependence, such as addiction or alcoholism. The δ receptor appears to deal with behavioural effects, although the δ and the κ receptors may also mediate analgesia.

Each opioid receptor, when coupled with an opiate, causes a specific biological response unique to that type of receptor. When an opiate activates more than one receptor, the biological response for each receptor is affected, thereby producing side effects. The less specific and selective an opiate may be, the greater the chance of causing increased side effect by the administration of the opiate.

Whereas morphine, which is a strong opioid analgetic agent shows effectiveness against strong pain by acting on the μ opioid receptor (agonist activity), there is a problem that its side effects such as nausea and neurologic manifestation including hallucination and derangement. Moreover, morphine forms psychological dependence, causing serious problems. Other side effects reported are respiratory depression, tolerance, physical dependence capacity, and precipitated withdrawal syndrome, caused by non-specific interactions with central nervous receptors.

WO 01/60823 describes 3,9-diazabicyclo[3.3.1]nonane derivatives with analgesic activity.

WO 01/72303 describes selective ligands for the δ opioid receptor.

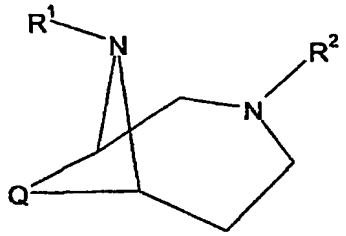
SUMMARY OF THE INVENTION

It is an object of the invention to provide novel compounds which act on opiate receptors.

A further object of the invention is the provision of compounds that substantially avoid the unwanted side effects associated with conventional peripherally acting analgesics.

It is a further object to provide compounds that bind selectively to the μ opioid receptor.

In its first aspect, the invention provides a compound of general formula I,



(I)

any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, wherein Q, R^1, and R^2 are as defined below.

In its second aspect, the invention provides a pharmaceutical composition, comprising a therapeutically effective amount of a compound of the invention, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

In a further aspect, the invention provides the use of a compound of the invention, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the opioid receptor.

In a still further aspect, the invention relates to a method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to modulation of the opioid receptor, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective

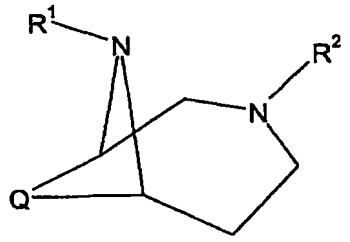
amount of a compound of the invention, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

Diazabicyclononane and -decane derivatives

In its first aspect, the invention provides a compound of general formula I,



(I)

any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof,

wherein

Q is $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$;

one of R^1 and R^2 is $-CH_2-CH_2-CH_2-R^3$, $-CH_2-CH=CH-R^3$, or $-CH_2-C\equiv C-R^3$;

wherein R^3 is aryl or heteroaryl;

which aryl and heteroaryl is optionally substituted with one or more substituents selected from the group consisting of:

halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, and alkynyl; and

the other of R^1 and R^2 is $-CO-R^4$;

wherein R^4 is alkyl, cycloalkyl, cycloalkylalkyl, aryl, or arylalkyl.

In one embodiment of the compound of general formula I, Q is $-CH_2-CH_2-$.

In a second embodiment of the compound of general formula I, Q is $-CH_2-CH_2-CH_2-$.

In a third embodiment of the compound of general formula I, one of R^1 and R^2 is $-CH_2-CH=CH-R^3$; wherein R^3 is defined as above. In a further embodiment, one of R^1 and R^2 is $-CH_2-CH_2-CH_2-R^3$; wherein R^3 is defined as above. In a still further embodiment, one of R^1 and R^2 is $-CH_2-C\equiv C-R^3$; wherein R^3 is defined as above.

In a further embodiment of the compound of general formula I, R^3 is optionally substituted aryl, such as optionally substituted phenyl. In a special embodiment, R^3 is phenyl.

In s special embodiment of the compound of general formula I, one of R^1 and R^2 is $-CH_2-CH=CH-R^3$; wherein R^3 is phenyl.

In a still further embodiment of the compound of general formula I, R^4 is alkyl. In a further embodiment, R^4 is aryl, such as phenyl. In a special embodiment, R^4 is methyl or ethyl.

In a further embodiment of the compound of general formula I,

Q is $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$;

one of R^1 and R^2 is $-CH_2-CH=CH-R^3$, or $-CH_2-C\equiv C-R^3$;

wherein R^3 is phenyl; and

the other of R^1 and R^2 is $-CO-R^4$; wherein R^4 is alkyl.

In a special embodiment the compound of the invention is

(±)-1-[9-(3-Phenyl-allyl)-3,9-diaza-bicyclo[4.2.1]non-3-yl]-propan-1-one;

(±)-1-[10-(3-Phenyl-allyl)-3,10-diaza-bicyclo[4.3.1]dec-3-yl]-propan-1-one;

(±)-1-[3-(3-Phenyl-allyl-3,9-diazabicyclo[4.2.1]non-9-yl]-propan-1-one;

or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

Any combination of two or more of the embodiments described herein is considered within the scope of the present invention.

Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Cycloalkyl means cyclic alkyl of three to seven carbon atoms, including but not limited to cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl;

Alkenyl means a group of from two to six carbon atoms, including at least one double bond, for example, but not limited to ethenyl, 1,2- or 2,3-propenyl, or 1,2-, 2,3-, or 3,4-butenyl.

Alkynyl means a group of from two to six carbon atoms, including at least one triple bond, for example, but not limited to ethynyl, 1,2-, 2,3-propynyl, or 1,2-, 2,3- or 3,4-butynyl.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Cycloalkoxy means O-cycloalkyl, wherein cycloalkyl is as defined above.

Cycloalkylalkyl means cycloalkyl as above and alkyl as above, meaning for example, cyclopropylmethyl.

Amino is NH_2 or NH-alkyl or N-$(alkyl)_2$, wherein alkyl is as defined above.

Aryl is a carbocyclic aromatic ring system such as phenyl or naphthyl (1-naphthyl or 2-naphthyl).

Heteroaryl is a 5- or 6-membered heterocyclic monocyclic group, for example, but not limited to, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol4-yl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-pyrimidyl or 6-pyrimidyl.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride, the hydrobromide, the nitrate, the perchlorate, the phosphate, the sulphate, the formate, the acetate, the aconate, the ascorbate, the benzenesulphonate, the benzoate, the cinnamate, the citrate, the embonate, the enantate, the fumarate, the glutamate, the glycolate, the lactate, the maleate, the malonate, the mandelate, the methanesulphonate, the naphthalene-2-sulphonate derived, the phthalate, the salicylate, the sorbate, the stearate, the succinate, the tartrate, the toluene-p-sulphonate, and the like. Such salts may be formed by procedures well known and described in the art.

Metal salts of a chemical compound of the invention include alkali metal salts such as the sodium salt of a chemical compound of the invention containing a carboxy group.

Steric Isomers

The compounds of the invention may exist in (+) and (-) forms as well as in racemic forms (±). The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the

present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Methods of Preparation

The chemical compounds of the invention may be prepared by conventional methods for chemical synthesis, e.g. those described in the working examples. The starting materials for the processes described in the present application are known or may readily be prepared by conventional methods from commercially available chemicals.

Also one compound of the invention can be converted to another compound of the invention using conventional methods.

The end products of the reactions described herein may be isolated by conventional techniques, e.g. by extraction, crystallisation, distillation, chromatography, etc.

Biological Activity

Compounds of the invention may be tested for their ability to bind to the μ, δ, and κ opioid receptors, e.g. such as described in example 2.

Compounds that bind to opiate receptors, in particular the μ receptor, are likely to be useful in the treatment of pain, postoperative pain, chronic pain (such as cancer pain and neuropathic pain), pain during labour and delivery, drug addiction (such as heroin addiction and cocaine addiction), and alcoholism.

Furthermore, compounds that bind to opiate receptors are also likely to be useful in the treatment of irritable bowel syndrome, constipation, nausea, vomiting, and pruritic dermatoses (itching), such as allergic dermatitis and atopy. Compounds that bind to opiate receptors have also been indicated in the treatment of eating

disorders, opiate overdoses, depression, smoking, sexual dysfunction, shock, stroke, spinal damage and head trauma.

Thus in further aspect, the compounds of the invention are considered useful for the treatment, prevention or alleviation of a disease, disorder or condition responsive to modulation of the opioid receptors, in particular the μ opioid receptor.

In a special embodiment, the compounds of the invention are considered useful for the treatment, prevention or alleviation of pain, postoperative pain, chronic pain, cancer pain, neuropathic pain, pain during labour and delivery, drug addiction, heroin addiction, cocaine addiction, alcoholism, irritable bowel syndrome, constipation, nausea, vomiting, pruritic dermatoses, allergic dermatitis, atopy, eating disorders, opiate overdoses, depression, smoking, sexual dysfunction, shock, stroke, spinal damage, or head trauma.

In a further embodiment, the compounds of the invention are considered particularly useful for the treatment, prevention or alleviation of pain, postoperative pain, chronic pain, drug addiction, alcoholism, and irritable bowel syndrome.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of a compound of the invention.

While a compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising a compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefore, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

The pharmaceutical composition of the invention may be administered by any convenient route, which suit the desired therapy. Preferred routes of administration include oral administration, in particular in tablet, in capsule, in dragé, in powder, or in liquid form, and parenteral administration, in particular cutaneous, subcutaneous, intramuscular, or intravenous injection. The pharmaceutical composition of the invention can be manufactured by any skilled person by use of standard methods and conventional techniques appropriate to the desired formulation. When desired,

compositions adapted to give sustained release of the active ingredient may be employed.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).

The actual dosage depend on the nature and severity of the disease being treated, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.1 to about 500 mg of active ingredient per individual dose, preferably of from about 1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.1 μg/kg i.v. and 1 μg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 μg/kg to about 10 mg/kg/day i.v., and from about 1 μg/kg to about 100 mg/kg/day p.o.

Methods of Therapy

In another aspect the invention provides a method for the treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disease, disorder or condition is responsive to modulation of the the opioid receptor, and which method comprises administering to such a living animal body, including a human, in need thereof an effective amount of a compound of the invention, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

It is at present contemplated that suitable dosage ranges are 0.1 to 1000 milligrams daily, 10-500 milligrams daily, and especially 30-100 milligrams daily, dependent as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further the preference and experience of the physician or veterinarian in charge. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.005 mg/kg i.v. and 0.01 mg/kg p.o. The upper limit of the dosage range is about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.001 to about 1 mg/kg i.v. and from about 0.1 to about 10 mg/kg p.o.

EXAMPLES

The invention is further illustrated with reference to the following examples, which are not intended to be in any way limiting to the scope of the invention as claimed.

Example 1

General: All reactions involving air sensitive reagents or intermediates were performed under nitrogen and in anhydrous solvents. Magnesium sulphate was used as drying agent in the workup-procedures and solvents were evaporated under reduced pressure.

9-Benzyl-9-azabicyclo[3.3.1]nonan-3-one and 8-benzyl-8-azabicyclo[3.2.1]nonan-3-one

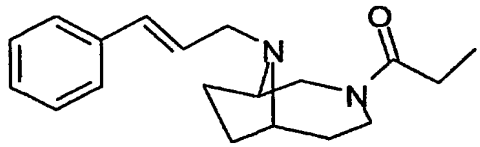
Were prepared according to Kashman, Y and Benary, E, J. Org. Chem., **37**, 3778, (1972).

9-Benzyl-3,9-diazabicyclo-[4.2.1]-nonane and 10-benzyl-3,10-diazabicyclo-[4.3.1]-decane

Were prepared according to 9-methyl-3,9-diazabicyclo-[4.2.1]-nonane [Michaels RJ and Zaugg HE, J. Org. Chem., **25**, 637, (1960)].

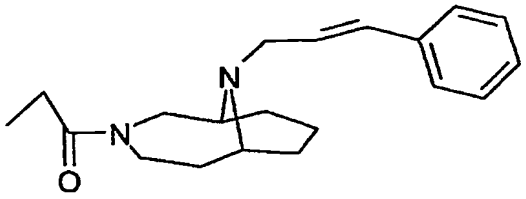
Method A

(±)-1-[9-(3-Phenyl-allyl)-3,9-diaza-bicyclo[4.2.1]non-3-yl]-propan-1-one hydrochloric acid salt (Compound a)



A mixture of 1-[9-H-3,9-diazabicyclo[4.2.1]non-3-yl]-propan-1-one (4.19 g, 23 mmol), potassium carbonate (3.45g, 25 mmol), cinnamylbromide (4.73 g, 24 mmol) and acetone (100 ml) was stirred at room temperature for 15 h. The mixture was evaporated, diethylether (100 ml) was added and the mixture was washed with water (50 ml). The crude product was converted to the hydrochloric acid salt by adding a mixture of hydrochloric acid in diethyl ether (10 ml, 2.8 M). The mixture was freeze dried for 70 h. The product was isolated as amorphous material (3.9 g, 49 %).

(±)-1-[10-(3-Phenyl-allyl)-3,10-diaza-bicyclo[4.3.1]dec-3-yl]-propan-1-one fumaric acid salt (Compound b)



Was prepared according to method A. The whole cascade from 10-benzyl-3,10-diazabicyclo-[4.3.1]-decane was performed in the same manner as from 9-benzyl-3,9-diazabicyclo-[4.2.1]-nonane. Mp 90 – 94 °C.

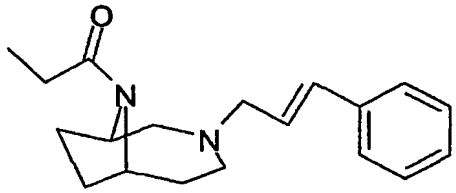
(±)-1-[9-H-3,9-diaza-bicyclo[4.2.1]non-3-yl]-propan-1-one (intermediate)

A mixture of 1-[9-benzyl-3,9-diazabicyclo[4.2.1]non-3-yl]-propan-1-one (7.4 g, 23 mmol), ethanol (100 ml, 99%), palladium on carbon (0.50 g, 10 %) was stirred under hydrogen for 1 h. The mixture was filtered through celite. Yield 4.47 g (100 %).

(±)-1-[9-Benzyl-3,9-diazabicyclo[4.2.1]non-3-yl]-propan-1-one

To a mixture of 9-benzyl-3,9-diazabicyclo[4.2.1]nonane (5.0 g, 23 mmol), diisopropylethylamine (4.35 ml, 25 mmol) in THF (50 ml) was added propionic acid anhydride (3.2 ml, 25 mmol) solved in THF (10 ml) over a time period of 10 min. The mixture was stirred at room-temperature for 1 h. The mixture was evaporated, aqueous sodium hydroxide (50 ml, 1M) was added and the mixture was extracted with diethyl ether (2 x 50 ml). The product was isolated as an oil. Yield 7.4 g (100 %).

(±)-1-[3-(3-Phenyl-allyl-3,9-diazabicyclo[4.2.1]non-9-yl]-propan-1-one hydrochloric acid salt (compound c)



A mixture of (±)-1-[3-H-3,9-diazabicyclo[4.2.1]non-9-yl]-propan-1-one (2.25 g, 12.3 mmol), cinnamylbromide (2.56 g, 13.0 mmol), potassium carbonate (2.07 g, 15.0 mmol) and acetone (100 ml) was stirred for 3 h at 55 °C. The mixture was evaporated, water (50 ml) was added and extracted with diethylether (2 x 50 ml). The crude product was converted to the hydrochloric acid salt by adding a mixture of hydrochloric acid in diethyl ether (5 ml, 2.8 M). The product was isolated as amorphous material (1.98 g, 48 %).

(±)-1-[3-H-3,9-Diazabicyclo[4.2.1]non-9-yl]-propan-1-one

A mixture of (±)-1-[3-*tert*-butoxycarbonyl-3,9-diaza-bicyclo[4.2.1]non-9-yl]-propan-1-one (4.5 g, 16 mmol), trifluoroactic acid (10 ml) and dichloromethane (50 ml) was stirred for 5 h. Aqueous sodium hydroxide (50 ml) was added and the mixture was extracted with dichloromethane (3 x 50 ml). Yield 1.9 g (79 %).

(±)-1-[3-*Tert*-butoxycarbonyl-3,9-diaza-bicyclo[4.2.1]non-9-yl]-propan-1-one

To a mixture of (±)-3-*tert*-butoxycarbonyl-3,9-diaza-bicyclo[4.2.1]nonane (4.5 g, 20 mmol), diisopropylethylamine (3.85 ml, 22 mmol) in THF (50 ml) was added propionic acid anhydride (2.82 ml, 22 mmol) solved in THF (10 ml) over a time period of 10 min. The mixture was stirred at room-temperature for 1 h. The mixture was evaporated, aqueous sodium hydroxide (50 ml, 1M) was added and the mixture was extracted with diethyl ether (2 x 50 ml). The product was isolated as an oil. Yield 4.7 g (84 %).

(±)-9-H-3-*Tert*-butoxycarbonyl-3,9-diaza-bicyclo[4.2.1]nonane

A mixture of (±)-9-benzyl-3-*tert*-butoxycarbonyl-3,9-diaza-bicyclo[4.2.1]nonane (14.2 g, 45 mmol), ethanol (150 ml, 99%), palladium on carbon (0.5 g, 10 %) was stirred under hydrogen for 1 h. The mixture was filtered through celite. Yield 10.56 g (100 %).

(±)-9-Benzyl-3-*tert*-butoxycarbonyl-3,9-diaza-bicyclo[4.2.1]nonane

To a mixture of (±)-9-benzyl-3,9-diaza-bicyclo[4.2.1]nonane (10.35 g, 47.9 mmol) triethylamine (7.5 ml, 53 mmol) and THF, was added slowly: boc-anhydride (11.5 g, 53 mmol). The mixture was allowed to react for 30 min. The solvent was evaporated. Diethylether (100 ml) was added and the mixture was washed with water (3 x 50 ml). Yield 14.5 g (96 %).

Example 2

Binding data

The compounds have been tested in binding assays using human recombinant opiate δ-, κ- and μ receptors. The assays were conducted as previously described by Simonin F et al [Simonin F et al, Mol. Pharmacol., 46(6), 1015-21, 1994], Simonin F et al [Simonin F et al, Proc. Natl. Acad. Sci. USA, 92(15), 7006-10, 1995], and Wang JB et al [Wang JB et al, FEBS Lett., 348(1), 75-9, 1994],

The test results are presented in Table 1 below.

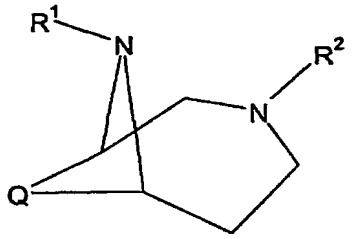
Table 1

Compound	δ	κ	μ
	K_i (μM)		
a	51% inhib at 10 μM	78% inhib at 10 μM	0.02
b	35% inhib at 10 μM	74% inhib at 10 μM	63% inhib at 100 nM
c	34% inhib at 10 μM	22% inhib at 10 μM	0.022

Furthermore, one compound, compound **b**, was tested for functional activity in guinea pig ileum. The assay was conducted as previously described by Maguire P et al [Maguire P et al, Eur. J. Pharmacol., 213(2), 219-25, 1992].
Compound **b** was determined to be a full agonist with an EC_{50} of 0.068 μM.

CLAIMS:

1. A compound of general formula (I),



(I)

any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof,
wherein
Q is $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$;
one of R^1 and R^2 is $-CH_2-CH_2-CH_2-R^3$, $-CH_2-CH=CH-R^3$, or $-CH_2-C\equiv C-R^3$;
wherein R^3 is aryl or heteroaryl;
which aryl and heteroaryl is optionally substituted with one or more substituents selected from the group consisting of:
halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, alkoxy, cycloalkoxy, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, and alkynyl; and
the other of R^1 and R^2 is $-CO-R^4$;
wherein R^4 is alkyl, cycloalkyl, cycloalkylalkyl, aryl, or arylalkyl.

2. The compound according to claim 1, wherein
Q is $-CH_2-CH_2-$.

3. The compound according to claim 1, wherein
Q is $-CH_2-CH_2-CH_2-$.

4. The compound according to any one of claims 1-3, wherein
one of R^1 and R^2 is $-CH_2-CH=CH-R^3$;
wherein R^3 is defined as in claim 1.

5. The compound according to any one of claims 1-4, wherein R^4 is alkyl.

6. The compound according to claim 1, wherein
Q is $-CH_2-CH_2-$ or $-CH_2-CH_2-CH_2-$;
one of R^1 and R^2 is $-CH_2-CH=CH-R^3$, or $-CH_2-C\equiv C-R^3$;
wherein R^3 is phenyl; and

the other of R^1 and R^2 is -CO-R^4;
wherein R^4 is alkyl.

7. A compound of claim 1 which is
(±)-1-[9-(3-Phenyl-allyl)-3,9-diaza-bicyclo[4.2.1]non-3-yl]-propan-1-one;
(±)-1-[10-(3-Phenyl-allyl)-3,10-diaza-bicyclo[4.3.1]dec-3-yl]-propan-1-one;
(±)-1-[3-(3-Phenyl-allyl-3,9-diazabicyclo[4.2.1]non-9-yl]-propan-1-one;
or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition, comprising a therapeutically effective amount of a compound of any one of claims 1-7, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, together with at least one pharmaceutically acceptable carrier, excipient or diluent.

9. The use of a compound according to any one of claims 1-7, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof, for the manufacture of a pharmaceutical composition for the treatment, prevention or alleviation of a disease or a disorder or a condition of a mammal, including a human, which disease, disorder or condition is responsive to modulation of the opioid receptor.

10. The use according to claim 9, wherein the disease, disorder or condition responsive to modulation of the opioid receptor is pain, postoperative pain, chronic pain, cancer pain, neuropathic pain, pain during labour and delivery, drug addiction, heroin addiction, cocaine addiction, alcoholism, irritable bowel syndrome, constipation, nausea, vomiting, pruritic dermatoses, allergic dermatitis, atopy, eating disorders, opiate overdoses, depression, smoking, sexual dysfunction, shock, stroke, spinal damage, or head trauma.

11. A method for treatment, prevention or alleviation of a disease or a disorder or a condition of a living animal body, including a human, which disorder, disease or condition is responsive to responsive to modulation of the opioid receptor, which method comprises the step of administering to such a living animal body in need thereof a therapeutically effective amount of a compound according to any one of the claims 1-7, or any of its enantiomers or any mixture of its enantiomers, or a pharmaceutically acceptable salt thereof.